REMARKS

A. Status of the Claims

Claims 1, 4-7, 9, 12-19, 21-48, and 53-57 were pending at the time of the Office Action. Claims 1, 4-7, 17, 21, 30, 48, and 53-57 have been canceled. Thus, claims 9, 12-16, 18-19, 22-29, and 31-48 are currently pending. Claims 9, 12, 13, 16, 18, 22-24, and 26 have been amended. No new matter was added by these amendments. Support for the amendments can be found in the specification at, for example, page 38, line 23 to page 39, line 7.

B. The Rejections Under 35 U.S.C. § 112 Are Overcome

1. Claims 1, 4-7, 9, 12-19, 21-48, and 57

The Action rejects claims 1, 4-7, 9, 12-19, 21-48, and 57 under § 112, first paragraph, as being indefinite and as lacking of written description. The Action asserts that dideoxynucleotides are not naturally occurring molecules, and that Applicants have not described any dideoxynucleotide analogs by structure or function. Thus, the Action asserts that the term "dideoxynucleotide analog" is not definite and lacks adequate written description. Applicants traverse this rejection.

The current claims recite a "dideoxynucleotide comprising a nucleotide analog." "Nucleotide" is defined in the specification at page 21, lines 26-28. The term "nucleotide" encompasses naturally occurring molecules. Those of skill in the art are familiar with nucleotide analogs. Numerous nucleotide analogs are described in the specification at, for example, page 21, lines 16-18; page 23, lines 15-29; Table 1 on pages 24-25; and page 25, line 7 to page 26, line 12. A person of ordinary skill in the art would understand the meaning of a dideoxynucleotide comprising a nucleotide analog. Applicants submit that the claims are

definite and are supported by adequate written description. Applicants, therefore, request the withdrawal of this rejection.

2. Claim 56

The Action rejects claim 56 under § 112, first paragraph, as being indefinite. Specifically, the Action asserts that it is not clear how one modifies or removes the Maxam and Gilbert treatment or variant thereof, if a further extension is to be performed. Claim 56 has been canceled, rendering this rejection moot.

C. The Rejections Under 35 U.S.C. § 102

Claims 53-54 and 57 were rejected under § 102(b) as anticipated by Short (WO 98/01581). Claims 53-54 were rejected under § 102(e) as anticipated by Stemmer (USPN 6,506,603) or, in the alternative, obvious under § 103. Claims 53-54 were rejected under § 102(e) as being anticipated by Carr. Claims 53-54 and 57 have been canceled, rendering these rejections moot. Furthermore, as discussed below, Carr is not available as prior art.

D. The Rejections Under 35 U.S.C. § 103(a) Are Overcome

1. The Legal Standard for Obviousness

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). When "the

motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper." MPEP § 2142. Moreover, the Federal Circuit Court has "consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir 1990); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

2. Carr Is Not Available As Prior Art

Carr is not available as prior art. Attached as Exhibit A to this paper is the signed Rule 131 Declaration of George L. Murphy and Robert A. Setterquist, and the unsigned, but approved, Rule 131 Declaration of Andrew D. Ellington. Applicants will submit a signed copy of Dr. Ellington's Declaration as soon as it becomes available. The declaration establishes that the inventors conceived of the claimed invention prior to the March 20, 2000 priority date of the Carr patent application, and were diligent in reducing the invention to practice up to and including the filing of the present application. Included with the declaration are pages describing all technological aspects of the invention from an invention disclosure made following Ambion, Inc. standard procedures prior to March 20, 2000. All of the work described in the declaration was performed in the United States.

Applicants, therefore, request the withdrawal of any obviousness rejections based on this reference.

3. Claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44, and 47 Are Patentable Over Short (WO 98/01581) In View of Short (U.S. Patent 6,361,974)

The Action rejects claims 1, 4-7, 9, 12-18, 21-22, 29-30, 32, 34-40, 43-44, and 47 as obvious over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974). Applicants traverse this rejection.

Claims 1, 4-7, 21, and 30 have been canceled, rendering this rejection moot as to these claim. Applicants submit that current claims 9, 12-18, 22, 29, 32, 34-40, 43-44, and 47 are patentable over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974).

The Action fails to establish a *prima facie* case of obviousness because the Action fails to show where the prior art teaches or suggest all of the elements of the claims. For example, the Action fails to show where Short (WO 98/01581) teaches defined primers; performing an extension in the presence of a dideoxynucleotide or a dideoxynucleotide analog; a plurality of first extended nucleic acids having essentially identical 5' ends and variable 3' ends; or modifying or removing the dideoxynucleotide or dideoxynucleotide analog from the first extended nucleic acids.

The Action asserts that the recitation of "defined primers" is not explicitly defined in the specification and, therefore does not distinguish the presently claimed invention over Short. Applicants note that claim language must be read in light of the disclosure and as understood by one of ordinary skill in the art. A "defined primer" is described in the specification at page 38, line 23 to page 39, line 7, and FIG. 1. As stated in the Declaration of Dr. Setterquist (Appendix A), based on the teachings of the present specification, a molecular biologist would understand that the term "defined primer" as used in the claimed method is a primer that generates extension products that share a defined 5' end (Declaration, para. 4). In particular, the specification states that "all or virtually all fragments will have 5' sequences defined by an initiating oligonucleotide" (Declaration, para. 5). The specification further states that in preferred methods, a pool of fragments are generated having "defined 5' ends and staggered, terminated ends, such that the lengths of the members preferably differ by a single nucleotide (FIG. 1)" (Declaration, para. 5). A review of FIG. 1 and the description of FIG. 1 on page 16 of the

specification illustrate the use of a "defined primer" as recited in the presently claimed methods (Declaration, para. 5).

Moreover, present claim 9 recites "a plurality of first extended nucleic acids having essentially identical 5' ends and variable 3' ends...." This further clarifies the meaning of the term "defined primers" in the present claims. The Action does not show where Short (WO 98/01581) teaches or suggests this aspect of the invention.

The Action also asserts that Short (WO 98/01581) teaches dideoxynucleotides or dideoxynucleotide analogs. The Action, however, fails to establish where Short (WO 98/01581) teaches or suggests the use of a dideoxynucleotide or dideoxynucleotide analog in a method as recited in the present claims. First, the Action has not identified a single location where Short (WO 98/01581) mentions a dideoxynucleotide. Rather, the Action asserts that one of ordinary skill in the art would understand that Short's use of the term "chain terminator" would be understood by those of ordinary skill in the art to encompass dideoxynucleotides. Applicants, however, would first point out that the term "chain terminator" only appears to occur in claims 1-3 of Short (WO 98/01581). Second, there does not appear to be any discussion or definition of "chain terminators" in Short (WO 98/01581). Finally, to construe the term "chain terminators" in Short's claims 1-3 to encompass dideoxynucleotides would result in the method being inoperative.

As further evidence, Applicants provide the Declaration of Dr. Setterquist, which states that although a molecular biologist would understand that the term "chain terminator" may include dideoxynucleotides and dideoxynucleotide analogs, a molecular biologist would not understand Short's use of the term "chain terminator" to include dideoxynucleotides and dideoxynucleotide analogs for the following reasons (Declaration, para. 6). First, Short does not mention

dideoxynucleotides or dideoxynucleotide analogs (Declaration, para. 6). Second, the mode of termination described by Short is different from the presently claimed method of using dideoxynucleotides or dideoxynucleotide analogs as chain terminating agents that are incorporated into the extending nucleic acid sequence (Declaration, para. 6). Moreover, Short's method recited in claims 1-3 would not appear to work with an agent that terminates chain elongation upon incorporation into an elongating chain, because subjecting the resultant polynucleotides to a second amplification would not be possible if the first amplification had been terminated with a dideoxynucleotide or dideoxynucleotide analog unless the polynucleotides' 3' OH was first restored (Declaration, para. 6). Dr. Setterquist's Declaration further notes that Short does not appear to teach this essential step (Declaration, para. 6).

The Action further alleges that DNA adducts function similarly to dideoxynucleotides. The Action, however, provides no factual basis for this assertion. As stated in the Declaration of Dr. Setterquist, a DNA adduct does not block the synthesis of the nascent strand by being incorporated into the nascent strand (Declaration, para. 7). Rather, a DNA adduct functions to block extension of the nascent strand by binding to the template strand (Declaration, para. 7). Thus, a DNA adduct does not function to block DNA synthesis in a manner similar to a dideoxynucleotide.

The Action also alleges that 5-bromouracil functions similarly to dideoxynucleotides to block amplification. The Action, however, provides no factual basis for this assertion. As stated in the Declaration of Dr. Setterquist, the incorporation of 5-bromouracil into an elongating nucleotide sequence does not terminate elongation (Declaration, para. 8). In contrast, the incorporation of a dideoxynucleotide into an elongating nucleotide sequence terminates elongation (Declaration, para. 8). A molecular biologist, therefore, would understand that 5-bromouracil and a dideoxynucleotide do not function similarly to terminate chain elongation (Declaration, para. 8).

The Action further cites Short '974 as teaching that modifying or removing a terminal nucleotide by EXO III enables subsequent extension reactions. Applicants note, however, that the Action did identify where Short '974 teaches modifying or removing a terminal ***dideoxynucleotide*** by EXO III to enable subsequent extension reactions. Regardless, Short '974 fails to address any of the shortcomings of Short (WO 98/01581) described above.

For the reasons described above, the Action failed to show where Short (WO 98/01581) teaches or suggests a number of elements of the present claims. The further reference to Short '974 also fails to teach or suggest all of the elements of the present claims. Applicants, therefore, request the withdrawal of this rejection.

4. Claims 19, 23-28, 31, 33, and 45 Are Patentable Over Short (WO 98/01581) In View of Short (U.S. Patent 6,361,974) and Further In View of Gelfand (U.S. Patent 6,346,379)

The Action rejects claims 19, 23-28, 31, 33, and 45 as obvious over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974) and further in view of Gelfand (U.S. Patent 6,346,379). Applicants traverse this rejection.

Applicants response in regard to Short (WO 98/01581) and Short (U.S. Patent 6,361,974) are presented above and are incorporated herein. The further reference of Gelfand fails to address the deficiencies in Short (WO 98/01581) and Short (U.S. Patent 6,361,974) described above. Therefore, a *prima facie* case of obviousness has not been established.

Applicants also note that Gelfand does not appear to teach that an α-phosphorothioate nucleotide is a functional equivalent of a ddNTP, as asserted by the Action. It appears to only be listed as one of several examples of unconventional nucleotides.

Furthermore, Gelfand appears to be directed to thermostable DNA polymerase. The Action did not present any reasoning as to why a person of ordinary skill in the art would have

been motivated to combine the teachings of Gelfand with the teachings of Short (WO 98/01581) and Short (U.S. Patent 6,361,974).

Applicants request that this rejection be withdrawn.

5. *Claims 41 and 42 Are Patentable Over Short (WO 98/01581) In View of Short (U.S. Patent 6,361,974) and Further In View of Mills (U.S Patent 5,064,754)*

The Action rejects claims 41 and 42 as obvious over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974) and further in view of Mills (U.S. Patent 5,064,754). Applicants traverse this rejection.

Applicants response in regard to Short (WO 98/01581) and Short (U.S. Patent 6,361,974) are presented above and are incorporated herein. The further reference of Mills fails to address the deficiencies in Short (WO 98/01581) and Short (U.S. Patent 6,361,974) described above. Therefore, a *prima facie* case of obviousness has not been established.

6. *Claims 46 and 55 Are Patentable Over Short (WO 98/01581) In View of Short (U.S. Patent 6,361,974) In View of Gelfand (U.S. Patent 6,346,379) and Further In View of Gish (Nuc. Acid Res (1987)*

The Action rejects claims 46 and 55 over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974) in view of Gelfand (U.S. Patent 6,346,379) and further in view of Gish. Applicants traverse this rejection.

Applicants response in regard to Short (WO 98/01581), Short (U.S. Patent 6,361,974), and Gelfand are presented above and are incorporated herein. The further reference of Gish fails to address the deficiencies in Short (WO 98/01581), Short (U.S. Patent 6,361,974), and Gelfand described above. Therefore, a *prima facie* case of obviousness has not been established.

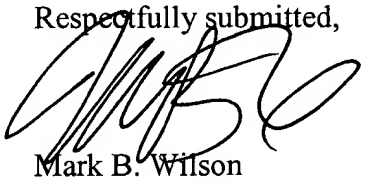
7. Claims 48 and 56

The Action rejects claims 48 and 56 over Short (WO 98/01581) in view of Short (U.S. Patent 6,361,974) in view of Wong (U.S. Patent 5,935,793) or Nikiforov (U.S. Patent 5,518,900). Claims 48 and 56 have been canceled, rendering this rejection moot.

E. Summary

In light of the preceding remarks, Applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should Examiner Spiegler have any questions regarding this response, please contact the undersigned at the telephone number listed below.

Respectfully submitted,



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